2. REMARKS/ARGUMENTS

2.1 STATUS OF THE CLAIMS

Claims 1-5, 7-31, 35, 39 and 40 were pending at the time of the Action.

Claims 1 and 14 have been amended herein.

Claims 41-43 have been added herein.

Claims 1-5, 7-31, 35, 39 and 40-43 remain pending in the case.

2.2 SUPPORT FOR THE CLAIMS

Complete support for the language of all pending claims can be found throughout the Specification and claims as originally filed. Applicants hereby certify that no new matter is incorporated by way of the accompanying amendment. New claims 41-43 are derived from pending claims 1 and 11, re-written and presented in independent format, in accordance with the Examiner's indication that the subject matter of claim 11 was patentable if included the limitations of the claim from which it depended.

Should any fees be deemed necessary in connection with the entry and consideration of the present paper the Commissioner is hereby authorized to deduct any necessary amounts from Deposit Account No. 08-1934, Order No. 36677.8.

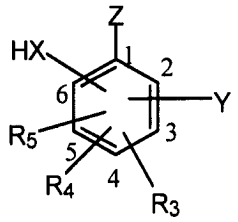
2.3 THE REJECTION OF CLAIMS UNDER 35 U. S. C. § 112, 2ND PAR., IS OVERCOME

The Action at pages 2-3, Items 4-7, rejected claims 1-5, 7-10, 12-31, 35, 39 and 40 under 35 U. S. C. § 112, 2nd paragraph, allegedly as being indefinite for "failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention."

Specifically, the Action in Item 5 rejects claim 1 (and its dependencies and related independent claims, 2-5, 7-10, 12-31, 35, 30 and 40 therefrom) as indefinite, allegedly because "it is not clear whether the term 'CH_2O- or CH_2S-' means that the XH group is 'CH_2OH or CH_2SH' or 'CH_3O- or CH_3S-,'" and "it is not clear what group is used for substitution, where is the substitution in the group, and what structures these substituted alkyl, aryl, arylalkyl or heteroaryl groups have" (*sic*).

Applicants respectfully traverse.

Claims 1 and 14 recite a method of cyclization of a peptide or peptidomimetic involving linkage to a cyclic aromatic auxiliary compound of General Formula II:



"in which X is oxygen, sulfur, CH_2O-, or CH_2S-"

Applicants direct the Examiner's attention to page 27 of the Specification, where it is stated that the compounds of the present invention comprise a hydroxy or a thiol substituent on the aromatic ring. Thus, the meaning of the terms objected to in claims 1 and 14 is clear, as a skilled artisan would appreciate that in order for the XH substituent to be either a "hydroxy" or a "thiol" moiety, in the instances where X is O, the term "XH" must represent a hydroxy group (*i.e.*, -OH). Similarly, in the instances where X is S, the term "XH" represents a thiol group (*i.e.*,

-SH). In those instances where X is -CH_2O-, the term "XH" represents a hydroxyethyl group (*i.e.*, -CH_2OH); and finally, in the instances where X is -CH_2S-, the term "XH" represents a thioethyl group (*i.e.*, -CH_2SH).

Applicants further contend that a fair reading of the Specification as a whole by one of skill in the peptide synthetic arts, would *not* lead such a person to interpret the "-XH" moiety as either "CH_3O-" or "CH_3S-", as suggested on page 3 of the Action, since such an interpretation would *not* result in the presence of an alcohol (*i.e.*, hydroxy; -OH) or a thiol (*i.e.*, -SH) moiety on the aromatic ring at position 2 or 3, as explicitly set forth in the specification at numerous points therein (see *e.g.*, page 41, para. 2, and page 27, para. 2 in particular). Applicants also note that none of the exemplary auxiliary compounds listed in Table 1 of the specification recite a "CH_3O-", or a "CH_3S-" moiety.

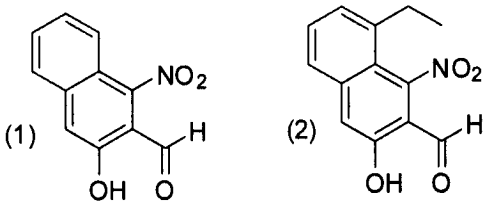
Second, with respect to the Examiner's query as to "what group is used for substitution, where is the substitution in the group, and what structures these substituted alkyl, aryl, arylalkyl or heteroaryl groups have" (*sic*), again Applicants respectfully traverse.

It is Applicants belief that such terms are clearly understood by one of ordinary skill in the peptide synthetic arts, and in particular, would be well-understood by such a skilled artisan having read and considered the teachings of specification as a whole. Applicants respectfully assert that the terms are <u>not</u> indefinite, and that the skilled artisan could make and use the auxiliaries in the methods described in the specification consistent with the recitation in claims 1 and 14.

Applicants also direct the Examiner's attention to the *International Union of Pure and Applied Chemistry*'s (IUPAC) definition of "substituent" which is viewable on the world-wide web at URL <u>http://www.chem.qmul.ac.uk/iupac/gtpoc/StSy.html#18</u>:

"Substituent: an atom or *group* of bonded atoms that can be considered to have replaced a hydrogen atom (or two hydrogen atoms in the special case of bivalent groups) in a parent *molecular entity* (real or hypothetical)." As the IUPAC is the governing body for, *inter alia,* the systematic nomenclature of compounds and compositions in the chemical arts, Applicants assert that the terms "substituted aryl," "substituted alkyl," "substituted arylalkyl" and "substituted heteroaryl" as recited in claims 1 and 14.

To further illustrate this point, Applicants provide the following compounds as examples of "substituted" auxiliaries that are within the scope of the present invention. Both the (1) aryl substituent and (2) substituted aryl substituent auxiliaries shown here would be readily considered to fall within the scope of the present invention. Indeed, a person of skill in the relevant art would also clearly recognize that these "substituted" derivatives still contain the core HnB auxiliary, and would also expect them to function in a manner analogous to that of the unsubstituted HnB auxiliary core.



Applicants also note for the record that the patent literature in the chemical arts is *full* of examples in which various optional substituents have been described and/or claimed (see *e.g.,* U.S. Patents 7,273,853, 7,247,625, 7,256,177, 7,253,194, 7,256,296, and 7,265,096). To that end, Applicants assert that the term is widely used in the chemical arts, and is therefore widely understood by a person of skill in such an art. Applicants respectfully request, therefore, that the outstanding rejection be withdrawn.

Finally, the Action in Item 6 rejected claim 14 (and its dependencies, claims 15 and 35) as indefinite allegedly because of the use of the term "c) on-resin cyclization" is confusing. The Examiner considers that it "is not clear what molecule is used in a method of on-resin cyclization."

Again, Applicants traverse, and respectfully note that one of skill in the art having considered the specification as a whole would well understand how the compounds of the invention could be linked so as to facilitate an on-resin cyclization of a selected peptide or peptidomimetic compound. In particular, Applicants direct the Examiner's attention to the specification, and at least on page 19, lines 28-30, which states that in one embodiment, the compounds may be attached to a solid support by covalently bonding the peptide or the peptidomimetic itself directly to the resin. This is also demonstrated schematically on pages 33 and 34 of the specification, and particularly in Example 1 where the use of Fmoc-Gly-WANG resin is discussed to synthesize (and subsequently de-protect) cyclic peptides or peptidomimetics on-resin. Additional teachings in this regard are also provided by Examples 2 and 3 (*N.B.* pages 35-37.

Alternatively, page 20, lines 4-7 and lines 23-25, teaches that the auxiliary may act as a linker to facilitate the linking of an "α-nitrogen of an (amino) acid residue in the desired peptide" (or peptidomimetic) to a solid support. Similarly, at page 21, lines 17 to 21, the specification illustrates this use in a schematic representation that teaches the use of particular auxiliary compounds as a linker to permits the use of standard protocols to assemble a linear peptide, or to synthesis C-terminal modified peptides.

Likewise, page 24 of the specification teaches at lines 1-20 that the auxiliaries of the invention may enable backbone linkage for the on-resin cyclization of a linear peptide or

peptidomimetic that may subsequently undergo side chain deprotection, and/or photolytic cleavage of the auxiliary to yield the final cyclized peptide.

Applicants thus respectfully disagree with the Examiner's assertion that it is not clear "what molecule is used in a method of on-resin cyclization." In fact, quite the opposite is true. The specification notes several exemplary embodiments involving on-resin cyclization (see, *e.g.*, page 18, line 34, bridging page 19, line 2; page 19, lines 25-36; page 20, lines 1-11; page 20 line 21 bridging page 21, line 3; and page 24, lines1, bridging page 25, line 5).

Applicants also note for the record that the term "on-resin cyclization' is frequently used in the literature. For example, three prominent papers in the same field as the invention have used the term within the actual text or as part of the title:

1. Spatola *et al.*, "Rediscovering an Endothelin Antagonist (BQ-123): A Self-Deconvoluting Cyclic Pentapeptide Library," *J. Med. Chem.*, **39:**3842-3846; 1996.

2. Bourne, "A Backbone Linker for BOC-Based Peptide Synthesis and On-Resin Cyclization: Synthesis of Stylostatin 1," *J. Org. Chem.*, **64:**3095-3101; 1999.

3. Rew *et al.*, "Solid-Phase Synthesis of Amine-Bridged Cyclic Enkephalin Analogues via On-Resin Cyclization Utilizing the Fukuyama-Mitsunobu Reaction," *J. Org. Chem.;* **67(25):**8820-8826; 2002.

To that end, Applicants believe the term is readily understood by one of skill in the related art, and that the present rejection is unwarranted; they now respectfully request that the rejection be withdrawn.

In summary, and for each of the aforementioned reasons, Applicants reiterate their earlier position that all pending claims are definite, and as such, respectfully request that these rejections be withdrawn.

2.4 THE OBJECTION TO CLAIM 11 IS RENDERED MOOT

The Action at page 3, Item 7, objected to claim 11, allegedly because the claim was dependent from a rejected claim.

Applicants respectfully traverse, and note for the record, now that the rejection of the base claim, claim 1, has been overcome, the objection to claim 11 is rendered moot. Applicants respectfully request therefore, that the objection be withdrawn, and that all pending claims be progressed to allowance.

2.5 CONCLUSION

It is respectfully submitted that all claims are fully enabled by the Specification, and that all claims are definite and free of the prior art. Applicants believe that the claims are acceptable under all sections of the Statutes and are now in condition for ready allowance, and that all of the concerns of the Examiner have been resolved. Applicants earnestly solicit concurrence by the Examiner and the issuance of a Notice of Allowance in the case with all due speed.

Applicants also note for the record their explicit right to re-file claims to one or more aspects of the invention as originally claimed in one or more continuing application(s) retaining the priority claim from the present and parent cases.

Should the Examiner have any questions, a telephone call to the undersigned Applicants' representative would be appreciated, in particular, in advance of any subsequent action on the merits.

Respectfully submitted,

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